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Highly Elevated Lactate Dehydrogenase Level in a Healthy Individual: A Case of Macro-LDH

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Macroenzymes are complexes of serum enzymes with a plasmatic protein. They have a higher molecular weight and a more prolonged serum half-life than those of unbound enzymes. Although macroenzymes may be found in the serum of post-myocardial infarction patients, they are not usually associated with any specific disease. Their presence, however, can cause an elevation in the serum levels of an enzyme, possibly leading to errors in diagnosis. We report a patient with extremely elevated serum levels of lactate dehydrogenase (LDH) due to the formation of complexes with immunoglobulin G. She had undergone a myriad of clinical examinations until the macroenzyme responsible for this finding was detected. We also review the literature on the clinical significance of macro-LDH. We propose that awareness of this rare and probably benign phenomenon can spare the patient from the distress of exhaustive investigations. Am. J. Hematol. 55:39–40, 1997. © 1997 Wiley-Liss, Inc.

Key words: lactate dehydrogenase; macroenzymes; immunoglobulin G

INTRODUCTION

While elevated levels of a serum enzyme are usually associated with a pathological condition, on rare occasions they may indicate the presence of a benign phenomenon known as a macroenzyme [1–3]. Macroenzymes are complexes of serum enzymes, proteins, immunoglobulins, or lipoproteins that have a higher molecular weight and a more prolonged serum half-life than are found in unbound enzymes [1,2,4]. They can be identified by electrophoresis [1–3,5]. Although the anomaly has been documented in the biochemical literature, only few physicians are aware of the existence of macroenzymes other than macroamylase.

We report a patient who presented with extremely high levels of serum lactate dehydrogenase (LDH) without any other evidence of disease. The patient underwent extensive clinical and laboratory investigations before the macroenzyme responsible for the LDH elevation was detected.

CASE REPORT

A 53-year-old woman was found to have LDH levels of 4457 U/L (normal range 297–618 U/L) during a routine medical examination. Physical examination and other blood tests, including a complete blood count (CBC), routine biochemistry assays, as well as B_{12} levels and thyroid function tests, were normal. In search for the source of the elevated LDH levels, she also underwent gastroscopy, colonoscopy and computerized tomography of the chest and abdomen, the results of all of which were normal. She was referred to the hematology clinic for additional tests.

The patient's general physical condition was excellent. She had no specific complaints and no past history of any disease. There were no signs of jaundice, lymphadenopathy, hepatosplenomegaly or skin lesions, and the examination of the heart and lungs was normal. Blood counts showed a hemoglobin level of 14.1 g/dl and white blood cells (WBC) of 6×10^3 cells/μl with a normal differential count. The platelet count was 240×10^9 cells/L, and the peripheral blood smear was normal. Biochemistry test results were all normal, except for the high LDH_3 levels, i.e., 1,236 U/L (normal range 160–320 U/L). Gel electrophoresis for serum LDH isoenzymes (LD vis isoen-

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zyme reagent, Helena Laboratories, Beaumont, TX) revealed a broad smeared peak of the LDH isoenzyme. Removal of serum IgG with an affinity chromatography Protein A-Sepharose CL-4B [3,5] markedly decreased the LDH levels, and repeated electrophoresis showed a near-normal pattern of the five LDH isoenzymes. These results are compatible with the presence of a LDH macroenzyme, i.e., IgG-LDH complex.

DISCUSSION

Macroenzymes are complexes of serum enzymes with a plasmatic protein [1,2,6]. Their existence was first reported by Wilding et al. [7], who described elevated levels of serum amylase due to an association of amylase and globulin. Since then, creatinine kinase (CK), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and aspartate aminotransferase (AST) were also reported to appear in a macroenzyme form [1,2,4,8–10]. For the most part, macroenzymes are composed of an enzyme–immunoglobulin complex; however, other forms of macromolecules (containing enzyme and a lipoprotein or enzyme oligomers) were observed as well [1]. The most common macroenzymes are macro-amylase and macro-CK [1,5].

LDH is a tetrameric enzyme that catalyzes the reversal reduction of pyruvate to lactate in the final step of glycolysis. Serum LDH is elevated in hemolysis, thromboembolism, systemic infection and inflammation, malignancy (especially lymphoproliferative and other hematological malignancies and malignant melanoma) and muscle injury. Macro-LDH appears in three forms: (1) a complex of LDH and immunoglobulin (IgA [representing 60% of all cases], IgG or IgM), (2) LDH and β-lipoprotein, and (3) self-association of the individual isoenzymes [1]. Macro-LDH may appear in electrophoresis as (1) an abnormal number of bands, (2) a change in the electrophoretic movement of LDH isoenzymes, and (3) widening of an existing band [11]. A higher molecular mass of macro-LDH causes a decrease in its renal clearance, resulting in prolonged elevation of the enzyme levels [1,12].

Macro-LDH was never reported as being associated with a specific disease state [1,2]. However, it may be frequently observed in the serum of myocardial infarction patients and occasionally in association with the development of Dressler's syndrome [1,2,4]. Galasso et al. [2] reported that about one-half of their patients with macro-LDH were diagnosed as having a concurrent acute myocardial infarction. The connection may be explained by the ''alteration of self-antigen theory,'' whereby an injury to the myocardium exposes the released cellular LDH to proteolytic activity in the plasma and the enzyme undergoes conformational change and becomes immunogenic [2,13]. The literature is inconclusive about an association between macro-LDH and autoimmune diseases. Sturk and Sanders [14] found macro-LDH that contained IgA in only 6 of 43 patients with autoimmune diseases. Galasso et al. [2] detected macro-LDH in 7 of 10 patients with rheumatologic diseases, but only three of them had an autoimmune disease. In another study on the incidence of macro-LDH in 100 patients with rheumatoid arthritis and systemic lupus erythematosus, the anomaly was detected in only one patient [15]. Pesce [16] concluded that no correlation could be established between the LDH IgG complex and any clinical disease state.

The phenomenon of macro-LDH is a rare one and usually constitutes a benign disorder despite the highly elevated enzyme levels. It may, however, present a diagnostic problem and awareness of its existence may spare the patient from undergoing a needlessly exhaustive clinical investigation.

REFERENCES

1. University of Virginia case conference: Macroamylase, macrocreatine kinase and other macroenzymes. Clin Chem 31:1243–1248, 1985.
2. Galasso PJ, Litin SC, O'Brien JF: The macroenzymes: A clinical review. Mayo Clin Proc 68:349–354, 1993.
3. Whelan PV, Malkus H: A macro creatine kinase isoenzyme is serum of apparently healthy individuals. Clin Chem 29:1411–1414, 1983.
4. Podlasek SJ, McPherson RA, Threatte GA: Specificity of autoantibodies to lactate dehydrogenase isoenzyme subunits. Clin Chem 31:527–532, 1985.
5. Urdal P, Landaas S: Macro creatine kinase BB in serum, and some data on its prevalence. Clin Chem 25:461–465, 1979.
6. Lang H, Wurzburg U: Creatine kinase, an enzyme of many forms. Clin Chem 28:1439–1446, 1982.
7. Wilding P, Cooke WT, Nicholson GI: Globulin-bound amylase: A cause of persistently elevated levels in serum. Ann Intern Med 60: 1053–1059, 1964.
8. Tozawa T: Enzyme-linked immunoglobulins and their clinical significance. Electrophoresis 10:640–644, 1989.
9. Fex G, Berntorp K: A circulating complex between ASAT and IgG in serum in an apparently healthy woman. Clin Chim Acta 164:11–15, 1982.
10. Artur V, Wellman-Bedbawska M, Jacquier A, Sies G: Complexes of serum gamma-glutamyltransferase with apolipoprotein and immunoglobulin A. Clin Chem 30:631–633, 1984.
11. Peters O, Gorus K, Van Camp B: NAD+ dissociable macromoleuclar lactate dehydrogenase. Clin Chem 28:1826–1827, 1982.
12. Levitt HD: Clinical use of amylase clearance and isoamylase measurement. Mayo Clin Proc 54:481–483, 1979.
13. Remaley AT, Wilding P: Macroenzymes: Biochemical characterization, clinical significance and laboratory detection. Clin Chem 35: 2261–2270, 1989.
14. Sturk A, Sanders GTB: Macroenzymes: Prevalence, composition, detection and clinical relevance. J Clin Chem Clin Biochem 28:65–81, 1990.
15. Biewenga J, Feltkamp TEW: Lactate dehydrogenase (LDH)-IgG_3 immunoglobulin complexes in human serum. Clin Chem Acta 64:101–116, 1975.
16. Pesce MA: The CK and LD macroenzymes. Lab Management Nov 29, 41, 1984.